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EXAMINER	
SCHNIZER, RICHARD A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/972,245	ROBERTS ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,41,42,44 and 47-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22, 41, 42, 44 and 47-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment after final rejection was received and entered on 5/20/09.

Claims 23-40 were canceled.

Claims 1-22, 41, 42, 44 and 47-64 are pending.

Claims 14-16 and 47-64 stand withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/10/03.

Claims 1-13, 17-22, 41, 42, and 44 are under consideration.

After further consideration, finality of the previous Office Action is withdrawn in favor of the following Non-Final Office Action.

Rejections not reiterated are withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 are rejected under 35 USC 103(a) as being unpatentable over the combination of Boos et al (Eur. J. Cancer 32A(9) : 1544-1550, 1996), Kawashima et al (Leukemia Res. 15(6): 525-530, 1991),

Ettinger et al (Cancer 75: 1176-1181, 1995), Saito et al (Leukemia (1997 Apr) Vol. 11 Suppl. 3, pp. 408-9), and Francis et al (Int. J. Hematol. 68(1): 1-18, 1998).

Boos studied the effects of using unmodified asparaginase from different sources, (*E. coli* or *Erwinia*) in the treatment of acute lymphoblastic leukemia because it was known that different asparaginase preparations had pharmacokinetic differences associated with increasing reports of hemorrhagic and thrombotic events. Boos stated that the pharmacologic aim of asparaginase treatment is the maximum reduction of asparagine concentration in patient's blood (page 1544, right column, lines 1-4), and made asparaginase activity the primary parameter for monitoring the effect of the drug on patients (page 1545, left column, lines 13-19). Patients were administered multiple doses of either of two *E. coli* asparaginase preparations, or of an *Erwinia* preparation, and asparaginase activity was assayed both before and after each administration. Boos established that the different preparations were not interchangeable, and found that each of the preparations provided different levels of activity after administration. See abstract and Figs. 1-4. Thus Boos provided a template and motivation for comparing the effects and activities of different preparations of asparaginase in vivo.

Kawashima reported on the treatment of patients with hematological malignancies with 2, 4 - bis(*o*-methoxypolyethylene glycol)-6-chloro-S-triazine-conjugated L-asparaginase (PEG_2-ASP). One patient, suffering non-Hodgkin's lymphoma, received treatment with unmodified L-asparaginase and suffered severe nausea, vomiting and loss of appetite. The patient went into remission, but later relapsed and was then treated with weekly or twice weekly intravenous infusion of

PEG_2-ASP, leading to complete remission within 2 months. The patient remained in complete remission for over one year with weekly infusions of PEG_2-ASP. During this period blood asparagine was assayed but was not detectable. Serum levels of asparaginase activity were measured throughout the course of treatment, before and after multiple administrations of PEG_2-ASP. See Fig. 1 on page 527 and Figs 2 and 3 on page 528. So, Kawashima taught a method of determining enzyme activity of PEG_2-ASP in serum derived from blood samples before, after, and between, multiple administrations of the drug. Determination of the asparaginase activity in serum is considered to be an assay of the asparaginase activity in the blood sample.

Ettinger reported the results of a multi-center study of monomethoxypolyethylene glycol succinimidyl)74-L-asparaginase (Oncaspar or PEG-L-asparaginase). Patients suffering from acute lymphoblastic leukemia, who had previously been treated with unmodified L-asparaginase, received PEG-L-asparaginase at days 1 and 14 of treatment. Two thirds of evaluable patients achieved complete remission. See Fig. 1 on page 1177, and page 177, column 2, under “Clinical Laboratory Evaluation”, and “Response Criteria”. See also page 1178, column 1, last two paragraphs.

Saito studied the antitumor activity of L-asparaginase modified with a comb-shaped copolymer of polyethylene glycol and maleic anhydride (PM-asparaginase). Mice were inoculated intraperitoneally with murine lymphoma cells, and then received unmodified L-asparaginase or PM-asparaginase. Five out of six mice treated with PM-asparaginase were alive at day 60 and were free of tumors. PM-asparaginase had

increased antitumor activity relative to unmodified asparaginase. See paragraph bridging pages 408 and 409.

Francis taught that bioactivity, stability, immunogenicity, and toxicity of a protein drug may be affected by the way in which the protein drug is PEGylated. See abstract, and pages 2-4. Francis also taught that PEGylation of protein drugs can cause toxicity. See sentence bridging columns 1 and 2 on page 4, and first sentence of paragraph bridging pages 7 and 8. Important considerations include the site of attachment of PEG, the degree of modification, the coupling chemistry chosen, the presence or absence of a linker, and generation of harmful co-products. See page 3, column 2, first full paragraph. Francis taught that the appropriate pegylation method is generally determined empirically by examining a range of different degrees of substitution, as well as different coupling techniques. See page 6, column 1, first full paragraph. The bioactivity retention and other functions of the products may be assessed as a mixture, or individual members of a PEGylation series may be assayed individually. See e.g. page 6, first full paragraph of column 1.

So, the prior art taught that the type and extent of PEGylation of therapeutic proteins could affect their activity and immunogenicity, such that it would be obvious to optimize these variables (see Francis above), and that PEGylation can also affect the bioavailability of the protein (see Ettinger at e.g. page 1176, column 2, second full paragraph of introduction). The cited prior art also taught three different forms of L-asparaginase (Kawashima, Ettinger, and Saito, respectively), each modified differently with a polyethylene glycol or a polyethylene glycol derivative, as well as a template for

comparing different preparations of asparaginase (Boos). Given that all three forms of L-asparaginase had anticancer activity, and that is was known that differently modified enzymes often had different pharmacokinetic characteristics such as activity and half-life, it would have been obvious to one of ordinary skill in the art at the time of the invention to compare each of these modified asparaginases just as Boos had compared unmodified asparaginases of differing preparations. One would have been motivated to do so to determine which preparation was most efficacious. In so doing it would have been obvious to follow the protocols of Kawashima or Boos in which the catalytic activity of L-asparaginase in blood was determined throughout the course of treatment. One would have been motivated to do so because the presence of that catalytic activity is what provides a therapeutic effect (see Boos above). One would have been further motivated to perform such a comparative study in view of the teachings of Saito, who indicated that differentially modified asparaginases had different performance characteristics, i.e. Saito taught that PM-asparaginase reduced immunoreactivities at lower degrees of modification than PEG_2-asparaginase. See Introduction on page 408. One of ordinary skill also appreciates that different modifications may lead to differences in enzyme activity, immunoreactivity, and circulation time (see Francis and Ettinger, above). Accordingly, it would have been obvious to perform comparisons of activity in vivo, as taught by Boos.

Claim 5 is included in this rejection because in light of the teachings of Francis, the extent of pegylation is a result-effective variable that is routinely optimized by those of skill in the art. See page 3, column 2, first full paragraph. Claim 6 is included in this

rejection because the selection of different coupling chemistries is part of the optimization process suggested by Francis, and different chemistries result in different modifying agents. For example, in the TMPEG method discussed at page 5, the PEG is linked to the polypeptide directly without any linker, whereas other chemistries may cause the introduction of immunogenic groups (see e.g. page 4, column 1, lines 1-10 of first full paragraph. Accordingly, it would be obvious to determine the relative catalytic activity of differently modified versions of L-asparaginase over the course of treatment, because there was reason to believe that some versions might be more or less active than others, and because it was routine in the art to make such measurements, as evidenced by Boos and Kawashima.

Claim 4 stands rejected under 35 USC 103(a) as being unpatentable over Boos, Kawashima, Ettinger, Saito, and Francis as applied to claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 above, and further in view of Petersen et al (US 6,531,122, of record).

The teachings of Boos, Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases. Francis also taught that one reaction chemistry known in the art for PEG modification utilizes a cyanuric chloride linker. See page 4, lines 5-9 of first full paragraph.

These references do not teach SBA-, SC-, and ALD-PEGs.

Petersen taught that SBA-, SC-, and ALD-PEGs, as well as a variety of other types of modified PEGs, including those with a cyanuric chloride linker, may be used interchangeably to modify polypeptide drugs. See paragraph bridging pages 24 and 25; column 25, first full paragraph, especially, lines 12, 27, 28, and 30; and column 26, lines 36-42.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify asparaginase with any of SBA-, SC-, and ALD-PEGs, because these derivatives were well known equivalents in the prior art. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, it was apparent from the teachings of Francis that bioactivity, stability, immunogenicity, and toxicity of a protein drug may be differentially affected by the way in which the protein drug is PEGylated. See abstract. Thus it would have been obvious to use different linkages in the process of optimizing these result-effective variables.

Thus the invention as a whole was prima facie obvious.

Claim 8, 11, and 20-22 stand rejected under 35 USC 103(a) as being unpatentable over Boos, Kawashima, Ettinger, Saito, and Francis as applied to claims

1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 above, and further in view of Abuchowski et al (Cancer Treat Rep 63(6): 1127-1132, 1979).

The teachings of Boos, Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach an enzyme used to treat viral infection, used to reduce glutamine levels, or asparaginase glutaminase from Pseudomonas.

Abuchowski taught treatment of tumors in mice by administration of *Achromobacter* glutaminase asparaginase rendered nonimmunogenic by modification with polyethylene glycol. The resulting enzyme had greatly enhanced half life in blood and increased the survival of experimental mice inoculated with tumor cells when compared with unmodified glutaminase asparaginase. Abuchowski measured asparaginase activity in blood over time after a single injection of enzyme, and also measured mouse weight throughout the course of treatment in which mice were given PEGylated enzyme on alternate days. See Figures 3 and 4 on pages 1130 and 1131.

It would have been obvious to one of ordinary skill in the art at the time of the invention to further study and compare differently modified *Achromobacter* glutaminase asparaginases in the process of optimizing PEGylation of this enzyme. One would have been motivated to do so because it was clear to those of ordinary skill in the art at the time of the invention that the amount and type of PEGylation was a result effective variable that influenced the activity of the enzyme as well as its serum half life and immunogenicity, as taught by Francis. In doing so it would have been obvious to

determine the activity of the differently modified drugs by assay of catalytic activity as taught by Boos, Kawashima, and Abuchowski. In comparing the performance of two differently modified enzymes over the course of treatment, one of ordinary skill would practice all of the claimed method steps, such that the invention as claimed would have been obvious.

Claim 19 stands rejected under 35 USC 103(a) as being unpatentable over Boos, Kawashima, Ettinger, Saito, and Francis as applied to claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 above, and further in view of Bollin et al (US 4,678,812, of record).

The teachings of Boos, Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach adding an excipient that protects asparaginase during lyophilization.

Bollin teaches that proteins can be stabilized by lyophilization and that saccharides are useful in stabilizing asparaginase during lyophilization.

It would have been obvious to one of ordinary skill in the art to add saccharides to the pegylated asparaginases developed by the methods described above, for the purpose of stabilizing them during lyophilization. One would have been motivated to do so because Bollin teaches that proteins may be stabilized by lypohilization, and that asparaginase in particular is stabilized by addition of saccharides during lyophilization.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 5/20/09 have been fully considered but they are not persuasive.

Applicant addresses the obviousness rejections at pages 13-15 of the response, asserting that the rejections are hindsight reconstructions.

Applicant asserts that the Examiner newly cites the Boos reference to supply motivation to use enzymatic activity as the metric by which to optimize the protection of an enzymatic therapeutic agent against host mediated inactivation, and that this cannot be done without employing hindsight. This is not true because, as indicated in MPEP 2144 (IV), the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In this case, the rejection suggests that it would have been obvious to one of ordinary skill in the art at the time of the invention to carry out the same active method steps that Applicant claims, without regard to necessarily preventing host mediated inactivation. The initial motivation for carrying out the steps would simply be to determine which variant of asparaginase provided the best therapy. In so doing, it would have been obvious to measure blood asparaginase activity in view of Boos, who taught that the pharmacologic aim of asparaginase treatment is the maximum reduction of asparagine concentration in patient's blood (page 1544, right column, lines 1-4), and who made asparaginase activity the primary parameter for

monitoring the effect of the drug on patients (page 1545, left column, lines 13-19). Note that Kawashima also measured asparaginase activity throughout the course of treatment, before and after multiple administrations of PEG_2-ASP. See Fig. 1 on page 527 and Figs 2 and 3 on page 528. Thus one need not, and the Examiner did not, depend on the alleged insight of Applicant regarding comparing host mediated inactivation of differently modified therapeutic agents in vivo. Note that in claim 1 step (e), all that is required to meet the claim limitation is to compare the biological activities of the first and second modified agents. The clause "to select..." etc. receives no patentable weight because it is not an active step, and merely represents something that is inherent in the active step of comparing the agents.

The claim preamble (determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer) has been given no patentable weight. Instead the Examiner has shown that the method steps claimed by Applicant would have been obvious if only one of ordinary skill had been interested in comparing different known forms of asparaginase.

Applicant asserts that it is unsurprising that a practitioner would formulate dose-response curves in an effort to formulate a uniform dosing regimen for an enzymatic therapy. The Examiner agrees, and notes that in fact Boos formulated comparative does response relationships for two different forms of asparaginase. The Examiner contends that this would have been obvious to do for any two or more differing forms of

asparaginase, including those disclosed by Kawashima, Ettinger, and Saito. It is simply in the best interests of patients to do so.

Applicant contends that nothing in the cited materials "suggests that such testing should be performed in the preclinical setting of research and development as the Examiner contends." The Examiner is not aware of contending that the method steps should be performed in the preclinical setting, and in fact there is no reason to make such a contention because there are no such limitations in the claims. If the steps were carried out in the clinic, as taught by Boos, to compare either the efficacy or the dose response curves of the enzymes of Kawashima, Ettinger, and Saito, the resulting method would meet all the claim limitations.

Applicant argues that Examiner engages in hindsight reconstruction by using Applicant's insight of abandoning conventional analyses of antigenicity, immunogenicity, and acceptable loss of bioactivity, and instead optimizing modification of therapeutic enzymes by evaluating the modified enzyme's capacity to catalyze it's reaction. This is unpersuasive because the distinction between analyzing acceptable loss of enzyme bioactivity and evaluating the modified enzyme's capacity to catalyze it's reaction is unclear. Furthermore, as indicated above, Applicant's motivation for putting together the recited method steps need not be the same as those that existed in the prior art. Nonetheless, if it would have been obvious to perform the same method steps for a different reason, then the invention is obvious. As a long as a rejection takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the

applicant's disclosure, it is proper. See MPEP 2145 (IX)(A). Applicant has not pointed to any claim limitation that was met by using knowledge gleaned only from the applicant's disclosure, and not the prior art. Applicant has instead, in effect, argued that the Examiner could not have combined the references for the same reasons that Applicant did without relying on Applicant's disclosure. A discussed above, the motivation for combining the references was not specifically to determine modification conditions for preventing host mediated inactivation of a therapeutic agent. Instead, the Examiner has found that it would have been obvious to combine the references in order to compare differently modified asparaginase to determine which was the most effective, or as Applicant points out, to determine dose-response curves.

Applicant argues at page 15 that the Examiner cherry-picked various steps used to determine the modification conditions from among countless combinations, when nothing in the cited material would have guided an artisan contemplating a method of determining the modification conditions of a therapeutic agent to prevent host mediated inactivation to a method of specifically measuring biological activity as claimed. This is unpersuasive. As noted above, it would not have been necessary for an artisan to have been contemplating a method of determining the modification conditions of a therapeutic agent to prevent host mediated inactivation in order to have combined the references in such as way as to render the claims obvious. One would have been motivated to combine the cited art in order to determine which of two or more differently modified asparaginases performed the best. In studying the effects of such drugs, it was routine to perform asparaginase assays over the course of treatment, between

drug administrations, as shown by Boos and Kawashima. The Examiner provided an example of researchers (Boos et al) comparing different asparaginase preparations known to have different pharmacological characteristics, in which the researchers measured asparaginase activities throughout the course of treatment. The Examiner provided examples of several differently modified asparaginases (Kawashima, Ettinger, and Saito), and also showed that it was known that the type and extent of modification can affect enzyme activity and other performance characteristics (Francis, Saito). So, one of ordinary skill would reasonably have expected differently modified asparaginases to have different pharmacokinetic parameters, possibly requiring different dosing regimens, and would have been motivated to compare them as taught by Boos. It would also have been obvious to measure other outcomes, such as blood asparagine levels, and the amounts of various blood cells, but this does not mean that it would not have been obvious to measure enzyme activity throughout the course of treatment, as taught by Boos and Kawashima. Note that Kawashima performed all of these assays (blood asparagine, blood asparaginase, and levels of various blood cells), such that one of ordinary skill would have considered performance of all of them to be routine, i.e. no selection would have been required.

Applicant reiterates the position that the rejection is of the type condemned by the courts in *Takeda Chem. Industs., Ltd. v. Alphapharm Pty, Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), and characterizes the Examiner's response as an assertion that the cited case law has no bearing on the instant case because the claims at issue therein concerned compositions, whereas the instant clams were directed to methods.

Applicant then asserts that the Examiner cites no case law or PTO rule for this distinction. In fact, the Examiner's response was somewhat more detailed, and stated that the analogy that Applicant attempted to make was unclear to the Examiner. The Examiner's response is essentially reiterated in the following three paragraphs.

It was the Examiner's understanding that Applicant was drawing a parallel between the claimed compound in *Takeda* and the step of measuring biological activity in the instant claims. In *Takeda* the cited prior art disclosed lead compounds from which, the court decided, it would not have been obvious to arrive at the claimed compound. In contrast, the instantly cited art discloses the precise means of measuring biological activity recited in the instant claims, i.e. Kawashima and Boos each measure activity of a modified enzyme after repeated administrations of the enzyme. What is missing from Kawashima and Boos is a comparison of two differently modified enzymes. However, the prior art disclosed several differently modified enzymes (Kawashima, Ettinger, and Saito), and motivation to compare them is provided by the recognition that activity can be affected differently by different modifications (Francis, Saito).

Applicant may have intended to argue that because the art taught that many outcomes could be measured in comparing two differently modified enzymes, it would not have been obvious to choose the enzyme activity assay of Kawashima (or Boos). In other words it would not have been obvious to select enzyme activity as an assay when other outcomes such as blood asparagine, tumor size, or the amounts of various types of blood cells could be measured as outcomes. This would have been unpersuasive

because, in fact, Kawashima used all of these assays. So, in essence, the analogs of all the lead compounds were selected by Kawashima for "further investigation". Applicant states at page 15 that "nothing in the cited material would have guided an artisan contemplating a method of determining the modification conditions of a therapeutic agent to prevent host-mediated inactivation to a method specifically measuring biological activity as claimed". As noted above, it would not be necessary to contemplate such a method in order to render the claims obvious.. The teachings of Kawashima would have led one of ordinary skill to assay all of the variables assayed by Kawashima, including asparaginase activity, when analyzing the usefulness of one or more variants of asparaginase,. Furthermore, the Boos reference provides motivation to measure asparaginase activity specifically, because it is "primary parameter" of drug monitoring in that study (see page 1545, left column , lines 17-19).

Applicant had argued previously that the cited material presents myriad timing options for conducting measurements, and that "nothing in the cited material hints of a method for determining the modification conditions of a therapeutic agent to prevent host mediated inactivation where a therapeutic agent is modified in two different ways and the biological activities of the two modified agents are compared *after each modified agent has been administered at least twice*" (emphasis in original). Applicant disqualified the teachings of Kawashima and Ettinger because they were not optimizing the modification level of a therapeutic agent, but instead were simply monitoring the effects of administered drugs over the course of treatment. This was unpersuasive. MPEP 2144 (IV) indicates that the reason for combining the references need not be the

same as that which motivated Applicant to make their invention. Thus the fact that Kawashima was simply monitoring the effects of the drug over the course of treatment is immaterial. The teachings of Kawashima and Boos would have suggested to one of skill in the art to measure blood asparaginase activity over the course of treatment when testing a modified asparaginase, or when comparing different asparaginases. It would have been obvious to compare differently modified asparaginases because several were known to exist, and because it was well known that different modifications could lead to different activities and efficacies.

Thus the Examiner made a reasonable attempt to consider Applicant's reliance on the cited case law, and to determine how it was relevant to the instant situation. The Examiner provided reasons why the case law was not analogous. The Examiner attempted to form analogies between the case law and the cited art, and showed why arguments based on such analogies were unpersuasive. Applicant did not respond to the reasoning presented by the Examiner, but merely stated that the Examiner's rationale was without foundation because it did not cite case law or PTO rule. This is unpersuasive because the Examiner need not cite case law or the MPEP when reason is sufficient.

For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Richard Schnizer/
Primary Examiner, Art Unit 1635